Technology

Fresh Approaches to a Familiar Problem: Skin Replacement

By JONATHAN D. BEARD

THE skin is the human body's largest organ, and perhaps the most vulnerable, too. It can recover quite well from cuts and other simple injuries. But accidents and diseases that destroy large areas of skin may exceed the body's ability to repair itself.

The traditional treatment, skin grafts from elsewhere on the patient's body, is painful — and painfully slow — and may not even be possible in severe burn cases because too little of the original skin survives.

Sensing a medical-market opportunity to shorten hospital stays, save lives and possibly make hundreds of millions of dollars in the process, the Lifecell Corporation, based in Woodlands, Tex., recently began selling a skin-replacement product to hospitals and burn centers. And three other companies — Organogenesis, Advanced Tissue Sciences and Biosurface Technology — are proceeding with clinical trials in hopes of receiving Food and Drug Administration approval for their own products.

The four are traded over the counter, and Dr. R. Brandon Fradd, a biotechnology analyst at Montgomery Securities, said, "The market is certainly large enough for all these companies."

Lifecell's product, Alloderm, which sells for $10,000 a square foot, uses skin taken from human cadavers that has been treated to avoid triggering the living patient's immune system. "Doctors have long known that skin from cadaver donors will temporarily 'take' and provide coverage over a wound or burn," said Dr. Stephen A. Livesey, Lifecell's chief scientific officer. "But they also know that such grafts will typically be rejected within 10 to 30 days."

Lifecell's process involves removing the outer, epidermal cells from the cadaver skin while retaining most of the rest of the structure, which forms a natural matrix for the patient's own tissue to grow into and over. Alloderm can be freeze-dried for storage and shipment, then rehydrated just before use.

Since Alloderm came on the market in December, only a handful of patients have been treated with it. Two of them — 4- and 5-year-old girls with burns over 25 percent and 40 percent of their bodies, respectively, were

somehow replaced. The standard treatment has been the "autograft," in which doctors remove a small patch of skin — epidermis and dermis — from another part of the patient's body, run it through a punch that expands its area by creating numerous holes, and then apply this graft to the cleaned wound. If all goes well, the graft closes the wound, and new tissue forms.

Unfortunately, taking each autograft causes a new wound, and people with large injuries can face months or years of agonizing surgery to cover the wound and recover from the "harvesting." In addition, the body tends to fill in the gaps between patches with scar tissue, which can so reduce flexibility that further surgery becomes necessary.

So doctors have long sought a skin replacement, tissue that could be stored at hospitals and burn centers, ready for use in closing wounds and speeding skin regeneration.

LIFECELL'S Alloderm was first to reach market because Federal rules do not demand formal clinical tests for donated human tissue, as opposed to artificial products. The lack of formal testing has engendered some controversy in the tiny skin-replacement industry about the safety of Lifecell's technique. Alloderm did, however, undergo 18 months of voluntary trials at 10 burn centers, said Jane Lea Hicks, Lifecell's vice president for business development. And she noted that the F.D.A. recently announced new regulations for tissue banks to make sure all donors are properly screened for transmittable diseases. Lifecell, Ms. Hicks said, complies with the new rules.

Organogenesis Inc. of Canton, Mass., is now in clinical trials at two dozen medical centers in the United States and has filed marketing applications in 18 European countries for its product, called Graftskin. (Its price is still undetermined.) Human fibroblast and keratinocyte cells are taken from foreskins that have been removed in circumcisions. The fibroblasts are mixed with purified collagen (a fibrous protein) taken from cows to form a matrix of connective tissue. The keratinocytes are then seeded onto this matrix, which grows in a nutrient medium into new tissue. When this tissue is placed on a patient's wound, its two layers encourage the body's own cells to migrate around, while enhancing the

Helping Skin Mend Itself

The various approaches to skin-replacement technology include Advanced Tissue Sciences' Dermagraft, now in human clinical trials.

NORMAL SKIN

Epidermis
Outer protective layer. Donor transplants of this layer tend to be rejected by the immune system, so to cover large wounds, grafts from other parts of the same patient must be used.

Pore — Hair

Dermis
Inner structural layer, made up of a collagen framework built by cells called fibroblasts. Transplants of this layer are not rejected.

Interior tissues such as muscles

REPLACEMENT DERMIS FROM THE LABORATORY

1 Cultured human fibroblasts
Living structural cells are recovered from skin tissue discarded when baby boys are circumcised.

Cells — Mesh

2 Cells deposited on a dissolvable mesh
Fibroblasts are seeded on a mesh of polyglactic acid, the same material used to make dissolving sutures for general surgery.

3 Cultured cells grow into a dermis
Using mesh as structural support, fibroblasts build up into a layer of living skin tissue. The mesh will dissolve after a few months in the body, when the graft has taken firmly.

USE IN A PATIENT

Epidermis autograft
A section of the top layer of skin is taken from elsewhere on the patient's body and perforated to allow it to stretch and cover a larger area.

Perforations

Interior tissues

Manufactured dermis graft
A section of living lab-grown dermis applied to the wound is intended to integrate with the patient's tissue and support the epidermis autograft.

Source: Advanced Tissue Sciences   Patrick J. Lyons/The New York Times

— about 400 people in the United States each year. He said his company was now concentrating on a product called Acticel. It is in clinical trials at more than 20 hospitals,

and Mr. Castaldi said that if it reaches the market it will sell for less than the $10,000 a square foot that Lifecell is charging for Alloderm.

Mr. Castaldi described Acticel as

"a living bandage." It too is created from epidermal skin tissue harvested from human foreskins, then attached to a gauze carrier and applied to burn wounds and chronic skin ulcers.

The competition in the field is just fine by Organogenesis's president, Thomas M. Tully, who sees plenty of space for all the players. "There is a huge market," he said.

The Executive Computer/John Markoff

Curtain's Rising on a Third Generation of On-Line Services

The Internet is going commercial with new hookups for PC's.

INDIAN WELLS, Calif.

THE fashionable joke floating around the Internet last week was that the "information super-highway is just like CB radio, but with more typing."

There is no disputing that computer networks and on-line services — spurred on in part by Vice President Al Gore and his promotion of the "national information infrastructure" — are currently the nation's biggest craze.

At Demo 94, a personal computer industry conference held here each year, a new generation of on-line services was on exhibit last week. The offerings won't be commercially available until later this year, but many of the technologies have already emerged in experimental form on the Internet, the global network of networks used by more than 15 million people.

And last week there were also fresh indications that the Internet is beginning commercial momentum, as major publishers begin to offer genuine commercial services over the net.

The first generation of on-line services, which emerged in the late 1970's, were based on connecting one's "dumb" terminal — a personal computer using terminal-emulator software — to a mainframe computer. Problems included a slow response time and a monitor display limited to simple screens of text.

The second generation — services like those from the Prodigy Services Company and America On-Line — have used the increasing power of the personal computer to speed up the interaction and give a simpler and more graphical interface to the user.

The next generation of on-line technology, exemplified by the new Interchange service that the computer trade publisher Ziff-Davis announced last week, is starting to emerge as computers grow even more powerful and communications links get faster.

The new systems promise to change the way users interact with remote central computers and, more significantly, are for the first time beginning to hint at an experience that rivals traditional print publishing.

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"This is truly the third generation in on-line technology," said Stewart Alsop, editor of Infoworld, a rival personal computer newspaper that has agreed to be distributed over the new Ziff-Davis service. "It begins to remove the notion of remoteness that came with earlier services."

Indeed, the old mainframe-to-dumb-terminal model of tele-computing appears to be giving way rapidly.

Earlier this month, General Magic, a Mountain View, Calif., software developer, unveiled Telescript, a communications language that will provide the foundation of A.T.&T.'s Personal Link on-line service, scheduled to begin later this year.
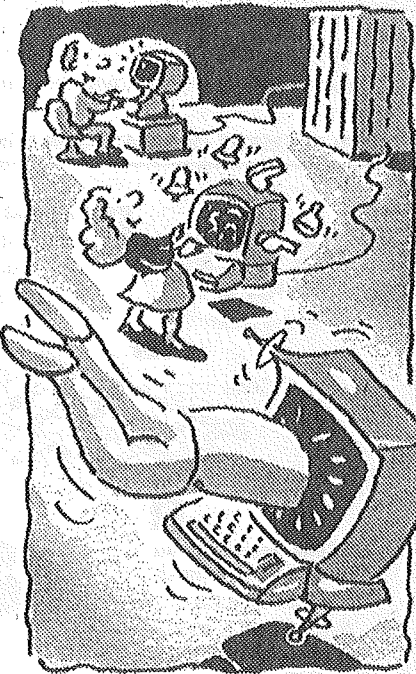
With Telescript, a computer user has no idea of "connecting" to a remote service at all. Instead, a program called an agent travels from the user's computer through the network, looking for information or even making purchases, based on commands given by the user.

Ziff-Davis is the largest publisher of computer magazines, and the Interchange service, which will be commercially available for Windows-based personal computers in the fall, offers its readers a way to read their favorite publications on-line, as well as the ability to join communities of other personal computer enthusiasts and download software and other information.

By itself that doesn't appear to be any more than what is available on existing on-line services, including Ziff-Davis's own Ziffnet, which is accessible through Compuserve.

But the Interchange system moves a step forward in taking advantage of the client personal computer. It offers the ability to view true "compound" documents that include graphics and images, rather than simple windows of scrolling text. It also offers multi-tasking, which means that you can start to download a document or a program in one part of the system and then go on to browse information in another part while the download is taking place, unattended.

Interchange, scheduled to go on-line next fall, makes extensive use of "hyper text" links between different pieces of information — a feature that is widely accessible in the Internet, but not available in more tightly compartmentalized commercial systems. As Interchange is designed, this means that it is possible to read a news article about a new computer system and then click on a pointer to read reviews about the same machine that are stored elsewhere.

No pricing information was available for Interchange, but the service will be sold via a fixed monthly membership fee for a specific number of hours, with additional hours sold on a metered basis.

The idea, said Michael Kolowich, president of Ziff-Davis Interactive, is to avoid the high costs that Prodigy encountered when it found that the service it envisioned as shopping in an electronic information-retrieval mall instead turned into an electronic community center where users chatted on-line for hours and hours, paying only a monthly flat fee. Prodigy subsequently changed to a pricing system pegged more closely to actual on-line time.

"You don't want to get into the trap that Prodigy got in when their best customers became their worst customers," Mr. Kolowich said.

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Another intriguing commercial venture introduced at Demo 94 was a joint venture between Dow Jones's electronic Dowvision news service and Wais Inc., a small software and services company.

Dowvision, which includes The Wall Street Journal and a variety of other newspapers and financial information, will be made available through Wais via the Internet for a monthly license or subscription fee. Next year, the service will also include The New York Times News Service, under an agreement signed last month by The New York Times Company and Dow Jones.

The Wais version of Dowvision should be a good example of third-generation on-line service. Users won't log in to Dow Jones at all. Instead they will be able to use a variety of "client" programs on their personal computers to more easily browse through and retrieve specific information from the Dowvision data base.

These client programs, which include Wais's own, as well as two free public-domain programs known as Gopher and Mosaic, display information in windows on an Apple Macintosh or on a Windows-based personal computer. The software eliminates many steps for the user, making many disparate data bases seem to be a single information bank. Retrieving specific stories is done by pointing with the mouse and clicking on a particular headline.

Dow Jones officials said the Wais joint venture is an experiment with electronic distribution over the Internet. For example, in a manner similar to the way newsstands work today, it will be possible to make the headlines of the day's top stories available for free for anyone on the Internet to browse. People who wanted to read the article, however, would have to pay for the "publication."

"We're looking at this as a way to learn about the Internet," said Greg Gerdy, assistant director of Dowvision. "The Internet is still the wild wild West."

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The big question, of course, is one the publishing world hasn't answered yet: Will electronic news services steal subscribers from traditional print publications?

Ziff-Davis executives said they hoped theirs would represent an obvious synergy between print publications and on-line services. "There are some things that print does well and some things that electronic media do better," said Mr. Kolowich of Ziff-Davis. "But we expect our print publications to be around for a long, long time." ■

Gary Zamchick

Sound Bytes/Glenn Rifkin

Tough-Talk Consultant To a Darwinian Industry

George Forrester Colony

Born: June 24, 1953; Keene, N.H.